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Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide

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ABSTRACT

The most recent epidemiological data on individual workers in the NIOSH and updated UCC occupational studies have been used to characterize the potential excess cancer risks of environmental exposure to ethylene oxide (EO). In addition to refined analyses of the separate cohorts, power has been increased by analyzing the combined cohorts. In previous SMR analyses of the separate studies and the present analyses of the updated and pooled studies of over 19,000 workers, none of the SMRs for any combination of the 12 cancer endpoints and six sub-cohorts analyzed were statistically significantly greater than one including the ones of greatest previous interest: leukemia, lymphohematopoietic tissue, lymphoid tumors, NHL, and breast cancer. In our study, no evidence of a positive cumulative exposure–response relationship was found. Fitted Cox proportional hazards models with cumulative EO exposure do not have statistically significant positive slopes. The lack of increasing trends was corroborated by categorical analyses. Cox model estimates of the concentrations corresponding to a 1-in-a-million extra environmental cancer risk are all greater than approximately 1 ppb and are more than 1500-fold greater than the 0.4 ppt estimate in the 2006 EPA draft IRIS risk assessment. The reasons for this difference are identified and discussed.

1. Introduction

Ethylene oxide (EO), a high production volume chemical and a raw material/intermediate in the production of many materials, is a direct-acting alkylating agent and a low potency mutagen that has been shown to be a low potency carcinogen in animal models. In 2006, the U.S. EPA prepared a draft cancer risk assessment for ethylene oxide (EO) based on their analysis of grouped data from the National Institute for Occupational Safety and Health (NIOSH) hospital sterilant cohort mortality study (Steenland et al., 2004) and failed to utilize the Teta et al. (1993) UCC cohort mortality study data on manufacturing workers exposed to EO. The Ethylene Oxide Review Panel of the EPA Science Advisory Board met on January 18 and 19, 2007, and made several recommendations to EPA, with the expectation that the draft would be revised. Specifically, the Panel recommended that EPA consider all of the epidemiology data including the UCC data. The UCC study has recently been updated to now include an average follow up of 37 years and an average cumulative exposure of 67 ppm-years (Swaen et al., 2009). Also, the Panel unanimously recommended that the EPA develop risk models based on direct analysis of the individual exposure and cancer outcome data for the NIOSH cohort, rather than using published grouped data. We, therefore, analyzed the UCC and NIOSH individual data separately and also combined them in order to increase the statistical probability of detecting any increase in cancer associated with EO exposure, to examine dose–response patterns, and to calculate excess environmental cancer risk. The combined cohorts include more than 19,000 workers, with a significant fraction relatively highly exposed and with long follow up.

2. Methods

All analyses were based on two datasets: (1) the most current NIOSH mortality data of sterilant workers (Steenland et al., 2004) and (2) the most current UCC mortality data of EO chemical manufacturing workers (Swaen et al., 2009). These two selected datasets were used both separately and in a pooled fashion for analyses in four stages: (1) traditional standardized mortality ratio (SMR) analyses, (2) dose–response modeling using a continuous cumulative exposure metric, (3) dose–response modeling using a categorical cumulative exposure metric, and (4) excess risk characterization.

2.1. Datasets

Only three EO epidemiology studies include quantitative exposure estimates that could be linked to individual cohort members (Steenland et al., 2004; Swaen et al., 2009; Hagmar et al., 1995).

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The population studied in Hagmar et al. (1995), however, was too young and the follow up too short (median 11.8 years) to be useful for our purposes. Because of their size, extensive periods of follow up, and available exposure estimates at the individual level, the NIOSH and UCC mortality datasets have the requisite attributes to become the basis for dose–response modeling. We have discussed this issue in greater detail elsewhere (Teta et al., 1999).

In 1991, NIOSH published the results of a cohort mortality study with follow up through 1987 of male and female sterilant workers with potential for exposure to EO (Steenland et al., 1991). Using measurements of EO concentrations from 1976 to 1985, job-exposure matrices with concentrations corresponding to each job and calendar-year combination were developed. Retrospective exposure reconstruction to estimate exposures before 1976 were based on regression modeling of important correlates of exposure (Greife et al., 1988; Hornung et al., 1994). The workers in the NIOSH cohort were from 14 different plants. One of these plants did not have enough data to develop reliable exposure estimates and its workers were excluded from dose–response analyses. The NIOSH data were more recently updated to include follow up through the end of 1998, for an average follow up of 26 years (Steenland et al., 2004). The same job-exposure matrix used in the original cohort was used for the updated cohort. The workers active at the end of 1987 (the end of the original follow up period) were assumed to stay working on the same job until their end of employment. This assumption did not substantially affect the cumulative exposures to EO because concentrations after the mid-1980s, following reduction in the OSHA PEL and ACGIH TLV-TWA, were much lower than the concentrations in earlier years. After excluding workers from the plant with no exposure information and workers lost to follow up, 17,493 workers remained in the NIOSH dataset. The NIOSH dataset analyzed herein includes 9859 female, 7634 male, 13,761 white and 3732 non-white workers. The breakdown of workers by plant, race, and sex for the NIOSH data is given in Table S1 in Supplemental materials.

Greenberg and Ott (1990) conducted a cohort mortality study of Union Carbide workers assigned to EO using or producing units in three locations with follow up through 1978. Teta et al. (1993) updated the UCC study to include follow up through the end of 1988. More recently, Swaen et al. (2009) updated the UCC study to include follow up through the end of 2003, for an average follow up of 37 years. The UCC cohort consists of 2063 male EO workers employed sometime between January 1, 1940, and December 31, 1988. The EO concentrations (i.e., the job-exposure matrix) for the UCC cohort have been developed and used in other publications (e.g., Teta et al., 1999; Kirman et al., 2004) and are well-documented in Swaen et al. (2009). EO exposure estimates were made for the period between 1925, when EO production started at the South Charleston Plant, and 1988. After 1988 EO exposures were negligible compared with earlier exposure levels and were therefore not included in the cumulative exposure assessment. EO production was phased out in 1972. The exposure estimates rely on the qualitative categorization of EO producing and using departments by exposure level, developed by Greenberg and Ott (1990) and on quantitative estimates of average intensity by these department categories and by time period 1925–1988, developed by Teta et al. (1993).

Table 1 shows the distributions of the observed cumulative EO exposures (ppm-days) at the end of follow up among the NIOSH females, NIOSH males, and UCC males. Table 1 shows that the UCC males had generally higher cumulative EO exposures than the NIOSH males. Also, the NIOSH females had substantial albeit lower exposures. For example, the 90th, 75th, and 50th percentiles for UCC males are approximately twice as large as the values for NIOSH males, and the 90th, 75th, and 50th percentiles for NIOSH females are at least half as large as the values for NIOSH males.

Table 1
Distribution of the cumulative EO exposures (ppm-days) at the end of follow up among the workers.

Percentiles		NIOSH Females	NIOSH Males	UCC Males
100.0	Maximum	293,538	642,925	422,933
99.5		107,249	239,777	250,489
97.5		45,363	102,167	135,224
90.0		19,420	38,687	72,643
75.0	Third quartile	7178	12,160	28,119
50.0	Median	1767	2807	7364
25.0	First quartile	520	668	1876
10.0		166	134	391
2.5		45	31	68
0.5		17	14	14
0.0	Minimum	5.1	4.9	2.1

In the 2006 EPA draft assessment, EPA did not pool the NIOSH study with the UCC study available at that time, expressing concerns that the UCC study cohort may have had confounding exposures. (Confounding is not thought to be a concern in the NIOSH study as the use of other chemicals in this work environment is limited.) In order for confounding to explain the absence of an exposure–response relationship in the UCC EO data, a subpopulation with low EO exposure would have to be at increased risk due to some other chemical exposure(s). This was, in fact, examined in the past and workers producing ethylene chlorohydrin were identified as a low EO exposure group with elevated risk for leukemia, NHL and pancreatic cancer. This sub-cohort of 278 workers were excluded from the UCC EO cohort and their mortality experience was reported separately (Teta et al., 1993). They are also excluded from the Swaen et al. update. No other potential confounders have been identified. A recent review of the available data led to the conclusion that pooling these studies appears to be acceptable and that differences with respect to exposure estimation and possible confounding do not negate the validity of a pooled analysis (Delzell, Toxicology Forum in 2009).

2.2. Endpoints of interest

Hogstedt et al. (1979) reported a cluster of three cases of leukemia among female sterilant workers: one chronic myeloid leukemia, one acute myelogenetic leukemia and one Waldenstrom leukemia. A large number of EO worker cohort mortality studies and updates followed this first report; these included 12 different groups of workers (including numerous facilities, hospitals, and plants) and over 33,000 workers in five countries. These have been reviewed in a detailed meta-analysis (Shore et al., 1993) and in an update to this meta-analysis (Teta et al., 1999). Although there was no consistent pattern of cancer mortality excesses in these studies, we examined endpoints that have been suggested as being associated with EO exposure in one or more of these epidemiology studies; namely, cancers of the stomach, breast, and pancreas, CNS cancers (and specifically brain cancer), lymphohematopoietic tissue (LH) cancers including leukemia (and specifically myeloid and lymphocytic leukemia), non-Hodgkin's lymphoma (NHL), multiple myeloma, and "lymphoid" cancers (a grouping developed in Steenland et al. (2004) that included non-Hodgkin's lymphoma, multiple myeloma, and lymphocytic leukemia). There were only a total of six workers with deaths caused by Hodgkin's lymphoma and only seven workers with deaths caused by bone cancer. Because these numbers are too small for meaningful dose–response modeling, neither bone cancer nor Hodgkin's lymphoma was included among the endpoints of interest herein. The only other endpoints for which SMRs were calculated in Steenland et al. (2004) and Swaen et al. (2009) are prostate, lung, kidney,

Table 2
Number of worker deaths for each endpoint by study and sex for workers with exposure information.

Endpoint	NIOSH and UCC			NIOSH			UCC
	Total	Male	Female	Total	Male	Female	Male
Lymphohematopoietic tissue	101	64	37	74	37	37	27
Lymphoid tumors[a]	70	44	26	53	27	26	17
Non-Hodgkin's lymphoma	42	30	12	30	18	12	12
Multiple myeloma	16	7	9	13	4	9	3
Lymphocytic leukemia	12	7	5	10	5	5	2
Myeloid leukemia	17	10	7	10	3	7	7
Leukemia	36	21	15	25	10	15	11
Central nervous system	27	19	8	14	6	8	13
Malignant brain neoplasm	25	17	8	13	5	8	12
Breast	103	1	102	103	1	102	0
Pancreas cancer	51	34	17	36	19	17	15
Stomach cancer	34	21	13	24	11	13	10
All causes	3800	2517	1283	2749	1466	1283	1051
All workers	19,556	9697	9859	17,493	7634	9859	2063
% Deceased	19	26	13	16	19	13	51
Person-years	526,212	265,174	261,038	450,906	189,868	261,038	75,306
Average follow up (person-years)	26.9	27.3	26.5	25.8	24.9	26.5	36.5

[a] Lymphoid tumors are defined herein in the same manner as in Steenland et al. (2004); namely, non-Hodgkin's lymphoma, multiple myeloma, or lymphocytic leukemia.

and coronary heart disease—none of which had statistically significantly increased SMRs and have not been suggested as being associated with EO exposure.

Table 2 shows the number of workers that died with each of the 12 endpoints analyzed for each study, sex, and combination of sex and study. The UCC male cohort includes fewer workers than the NIOSH male and female cohorts. However, the UCC cohort is much older with an observation start date of 1940 and 10 years longer average length of follow up. As a consequence, the percentage of deceased workers in the UCC cohort (51%) is more than three times higher than the percentage of deceased workers in the NIOSH cohort (16%), resulting in comparable numbers of male deaths in the health outcomes of greatest interest. Although the UCC cohort has fewer workers than the NIOSH cohort, it is a much older cohort with substantial person-years at risk (see Table 2) at older ages and statistical power on its own, thereby increasing the power of the pooled analyses.

Table S2 in Supplemental materials shows the 12 cancer endpoints with the corresponding cause of death codes (ICD) and the calendar-year intervals for which the ICD codes were applicable.

2.3. Statistical analyses

SMRs were calculated in the standard manner as the ratio of observed to expected numbers of deaths. The expected values for the NIOSH and UCC cohorts were taken from Steenland et al. (2004) and Swaen et al. (2009), respectively. For the NIOSH cohort, life-table analyses were conducted using the NIOSH life-table program (Steenland et al., 1998), which allows for calculations of SMRs for 99 causes of death for the years 1960–1999. For the UCC cohort, the statistical analysis was performed by means of OCMAP (Marsh et al., 1998), a statistical program that includes subroutines specifically developed to analyze cohort studies based on a modified life-table procedure. Tables S3–S8 list calculations and values for the observed and expected numbers, the SMR, and a two-sided 95% confidence interval on the SMR.

For dose–response modeling, we fit Cox proportional hazards models with cumulative EO exposure (ppm-days) as the predictor variable to the data on individual exposures and cancer outcomes for each combination of 12 cancer mortality types of past interest and for six sub-cohorts (NIOSH males, UCC males, NIOSH and UCC males, NIOSH females, NIOSH males and females, and NIOSH and UCC males and females). The effect was modeled as a linear function of cumulative EO exposure (ppm-days) treated as a continuous variable. Age was the index variable used to identify the risk sets in the Cox regression. Because we found no covariates that were more than rarely statistically significant, no covariates (other than race for the NIOSH data) were included. The NIOSH dataset had workers classified as white (13,671), black (3105), Oriental (401), Hispanic (38), other (3), and unknown (185). The UCC dataset had the workers classified as white or Caucasian (1510), black (2), non-white (28), and unknown (523). The analyses of the NIOSH data were adjusted for race, but the analyses of the UCC data did not adjust for race because of the substantial uncertainty of the race classification. Each study and sex were fit separately as well as combined. In pooled analyses, study and sex were treated as covariates. Both lagged and unlagged analyses were conducted. The proportional hazards assumption in the Cox modeling herein was checked by testing for an interaction between the exposure metric and age in all combinations (69) of the 12 endpoints and six sub-cohorts analyzed. There was no statistically significant interaction (at the 5% significance level) in any of the 69 combinations using Wald's Test and only 2 out of 69 were significant using the likelihood ratio test.

Categorical dose–response analyses were added to augment the search for dose–response information beyond the log-linear model in the Cox proportional hazards models and to complement the categorical analyses in Steenland et al. (2004) and considered in EPA's 2006 draft assessment. Hazard rates (per person-year) at different exposure categories were compared to the hazard rate for the lowest exposure category. The dose range for each combination of study, sex, and endpoint was partitioned into five categories of the cumulative exposure to EO of the workers with the response, with approximately equal number of responses per category. The number of categories was five or fewer, defined in such a way that there would be at least two responses (deaths from the cause of interest) per category whenever the total number of deaths with the endpoint was more than three.

Following common U.S. EPA regulatory practice, we use the fitted Cox proportional hazards models to characterize excess environmental cancer risk. We incorporate the EPA (2005b) guideline's default age-dependent adjustment factors (ADAFs)[1] and computational procedures for age-dependent cumulative expo-

[1] *Abbreviations used:* ADAFs, age-dependent adjustment factors; EC, effective concentration; EO, ethylene oxide; EPA, U.S. Environmental Protection Agency; ICD, International Statistical Classification of Diseases and Related Health Problems; LEC, 95% lower confidence limit on the effective concentration; LH, lymphohematopoietic; MLE, maximum likelihood estimate; NIOSH, National Institute of Occupational Safety and Health; PoD, point of departure; RR, rate ratio; SMR, standardized mortality ratio; UCC, Union Carbide Corporation.

sures. These models estimate effective concentrations (ECs) corresponding to a 1-in-a-million excess environmental cancer risk. We contrast our analyses with that proposed by EPA (2006) based solely on grouped data for NIOSH males and one cancer mortality endpoint.

3. Results

3.1. SMR analyses

Steenland et al. (2004) and Swaen et al. (2009) present SMR analyses of the NIOSH and UCC cohorts, respectively, for several endpoints. Table 3 provides a consolidated overview of the SMRs for the six sub-cohorts. The details of the SMRs are in Tables S3–S8 in Supplemental materials. As discussed in Steenland et al. and Swaen et al., except for bone cancer, none of the SMRs were statistically significantly greater than one.

3.2. Dose–response modeling

Table 4 summarizes the findings with respect to the estimated slopes in the unlagged Cox proportional hazards models. (Lagged results were similar, e.g., see Table S10.) More details are given in the last column of Table S9 in Supplemental materials which shows the number of workers, number of deaths, maximum likelihood estimate (MLE) and standard error (SE) of the slope parameter multiplying cumulative EO exposure in the Cox proportional hazards model, and the slope's p-value for each of the 12 endpoints and for each analyzed combination of sex and study.

None of the dose–response models for the 12 endpoints and six sub-cohorts analyzed herein resulted in a statistically significant positive estimated slope. Also, as shown in Table 4 and as would be expected in the case of no dose–response relation, the maximum likelihood estimates of the slopes were approximately half positive and half negative. None of the estimated slopes that were positive were statistically significant, and none of the 12 endpoints had positive estimated slopes for all six sub-cohorts.

3.3. Categorical analyses

Cox proportional hazards models that treat cumulative EO exposure as a continuous variable indicated that there were no statistically significant increasing trends. The lack of increasing trends is corroborated by the categorical analyses.

Table 5 shows, for each combination of study, sex, and endpoint, the rate ratios that are statistically significantly different from zero at the 5% significance level. In Table S9 in Supplemental materials, there are five columns (one for each of the five or fewer categories) indicating the cumulative exposure interval (ppm-days), number of workers at risk, number of deaths, the estimated rate ratio, a two-sided 95% confidence interval on the rate ratio, and p-value for the rate ratio being non-zero.

There were statistically significant rate ratios only when the number of categories was five. All of the statistically significant categories had increased rates; none had decreased rates. There are nine cases in which the rate ratios (approximately 4%) are statistically significant at the 5% significance level. Most of these nine cases correspond to the highest dose range (the 5th category). The concentrations in these categories greatly exceed potential environmental levels and also exceed the OSHA PEL of 1 ppm TWA. There is no suggestion of a dose–response trend, in the sense that there is no case in which the rate ratio is statistically significant in the two highest categories, nor in any two consecutive categories. In addition, none of the slopes of the Cox proportional hazards models that were fit to the continuous exposure data indicated a statistically significant positive trend with increasing cumulative exposure to EO.

The results of the rate ratios presented herein cannot be directly compared with those given in Steenland et al. (2004) because they analyzed odds ratios instead of rate ratios and they used quartiles instead of quintiles. Also, the Steenland et al. odds ratios cannot be reproduced because they used a randomly selected subset of the risk set instead of the full risk set. (The full risk set is used herein in the standard Cox proportional hazards model.) However, the conclusions of the categorical analyses in Steenland et al. (all of which were based on cumulative exposure) are consistent with the conclusions drawn here for the NIOSH cohort.

3.4. Excess risk characterization

None of fitted Cox proportional hazards models herein for any of the 72 combinations of the 12 endpoints and the six sub-cohorts found statistically significant increases (statistically significant positive slopes) with increased cumulative EO exposure

Table 3
Standardized mortality ratios (SMRs).

Cause of death	NIOSH males and females and UCC males combined[a]	NIOSH and UCC combined: males[a]	NIOSH males and females combined[a,b]	NIOSH females[a,b]	NIOSH males[a,b]	UCC males[c]
All causes	0.89*	0.90*	0.90*	0.86*	0.94*	0.85*
All cancers	0.97	0.94	0.98	0.92	0.94	0.95
All hematopoietic	0.97	1.00	1.00	0.91	1.09	0.89
Non-Hodgkin's lymphoma	1.01	1.18	1.00	0.73	1.29	1.05
Hodgkin's lymphoma	0.92	1.13	1.24	0.47	1.83	0.00
Brain	0.85	0.98	0.59*	0.65	0.52	1.64
Leukemia	0.97	0.95	0.99	1.02	0.97	0.93
Pancreas	0.93	1.00	0.92	0.82	1.03	0.96
Stomach	1.06	0.93	1.07	1.34	0.87	1.02
Breast cancer	0.99	2.04	0.99	0.99	2.04	NA
Prostate	1.05	1.05	1.29	NA	1.29	0.81
Lung	0.99	0.96	1.05	1.05	1.05	0.86
Kidney	1.25	1.46	1.19	0.78	1.51	1.40
Bone	2.48	2.36	2.82**	2.04	3.51	1.37
Coronary heart disease	0.90*	0.94	0.92*	0.87*	1.04	0.86*

NA, not applicable.
[a] The NIOSH data includes all workers even those with no exposure information.
[b] From Table 1 of Steenland et al. (2004).
[c] From Table 2 of Swaen et al. (2009).
* SMR is statistically significantly less than one at the 5% significance level.
** SMR is statistically significantly greater than one at the 5% significance level.

Table 4
Slopes of estimated cancer-specific mortality rates with respect to cumulative exposure to EO: positive and negative non-statistically significant slopes and statistically significant negative slopes.[a]

Endpoint	Males			Females	Males and females	
	NIOSH	UCC	NIOSH and UCC	NIOSH	NIOSH	NIOSH and UCC
Lymphohematopoietic tissue	+ns	−ns	+ns	−ns	+ns	+ns
Lymphoid tumors	+ns	−ns	+ns	−ns	+ns	+ns
Non-Hodgkin's lymphoma (NHL)	+ns	−ns	+ns	−ns	+ns	+ns
Multiple myeloma	−ns	**−SS**	−ns	−ns	−ns	−ns
Lymphocytic leukemia	+ns	−ns	+ns	−ns	+ns	+ns
Myeloid leukemia	−ns	−ns	−ns	−ns	**−SS**	−ns
Leukemia	+ns	+ns	+ns	**−SS**	+ns	+ns
Central nervous system	−ns	**−SS**	**−SS**	+ns	−ns	−ns
Malignant brain neoplasm	−ns	**−SS**	−ns	+ns	−ns	−ns
Breast	−ns[b]	n/a	−ns	+ns	+ns	n/a
Pancreas cancer	−ns	+ns	−ns	+ns	−ns	−ns
Stomach cancer	−ns	+ns	+ns	−ns	−ns	+ns

n/a indicates that no males in UCC study had breast cancer.

[a] A positive sign (+ns) indicates that deaths increase (but not statistically significantly) with increases in the cumulative exposure to EO while a negative sign (−ns) indicates that deaths decrease (but not statistically significantly) with increases in the cumulative exposure to EO. −SS implies that the maximum likelihood estimate (MLE) of the parameter is statistically significantly less than zero at the 5% or 1% significance level.

[b] Result is based on only one breast cancer death in male NIOSH workers.

(lagged or unlagged) at the 5% significance level. Nevertheless, we used these same models and applied EPA's (2005a) guideline quantitative risk assessment procedures to characterize excess risk for a continuous lifetime exposure to a constant environmental concentration even though the positive slopes were not statistically significant.

Table 5
Categorical analysis: quintiles of cumulative EO exposure with statistically significantly increased response rates compared to the lowest quintile.[a,b,c]

Endpoint	Males			Females	Males & Females	
	NIOSH	UCC	NIOSH & UCC	NIOSH	NIOSH	NIOSH & UCC
Lymphohematopoietic Tissue						
Lymphoid Tumors						
Non-Hodgkin's Lymphoma (NHL)						
Multiple Myeloma						
Lymphocytic Leukemia						
Myeloid Leukemia						
Leukemia						
Central Nervous System						
Malignant Brain Neoplasm						
Breast						
Pancreas Cancer						
Stomach Cancer						

[a] A shaded cell indicates a cumulative EO exposure quintile in which there was a response rate statistically significantly greater than the response rate in the lowest (first) quintile. For example, for lymphohematopoietic tissue in the NIOSH male cohort, the 5th quintile of five quintiles (i.e., the interval with the highest cumulative exposures) had a response rate that was statistically significantly greater than the response rate in the lowest quintile at the 5% significance level.

[b] Every quantile for every combination of the 12 endpoints and the six sub-cohorts was evaluated. Blank cells for an endpoint-sub-cohort combination indicate that there no quantiles with statistically significantly increased response rates compared to the lowest quantile.

[c] Although all of the statistically significant response rates occurred when there were five cumulative exposure quantiles, a few cells had less than five quantiles because there were fewer than 10 responses (fewer than two responses for each of five quantiles).

Table 6
Maximum likelihood estimate (MLE) of the EC(1/Million): MLE of the environmental concentration in ppm corresponding to an extra risk of 0.000001.[a,b]

Endpoint	Males			Females	Males and females	
	NIOSH	UCC	NIOSH and UCC	NIOSH	NIOSH	NIOSH and UCC
Lymphohematopoietic tissue	0.0006		0.0010		0.0009	0.0019
Lymphoid tumors	0.0006		0.0010		0.0008	0.0015
Non-Hodgkin's lymphoma (NHL)	0.0012		0.0017		0.0015	0.0023
Multiple myeloma						
Lymphocytic leukemia	0.0013		0.0016		0.0019	0.0024
Myeloid leukemia						
Leukemia	0.0018	0.0116	0.0023		0.0078	0.0092
Central nervous system				0.0028		
Malignant brain neoplasm				0.0019		
Breast[c]				0.0007	0.0017	0.0017
Pancreas cancer		0.0012		0.0012		
Stomach cancer		0.0011	0.0034			0.0059

[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration.
[b] A blank cell implies that the estimated dose–response relationship was non-increasing.
[c] There were no males in the UCC cohort with a breast cancer mortality; hence, no dose–response modeling was done for the UCC cohort. There was one male in the NIOSH male cohort who had a breast cancer mortality; hence, dose–response modeling (albeit very uncertain) was done for the NIOSH male cohort.

Table 7
Lowest effective concentration [LEC(1/Million)]: 95% lower confidence limit on the environmental concentration in ppm corresponding to an extra risk of 0.000001.[a,b]

Endpoint	Males			Females	Males and females	
	NIOSH	UCC	NIOSH and UCC	NIOSH	NIOSH	NIOSH and UCC
Lymphohematopoietic tissue	0.0003	0.0006	0.0004	0.0004	0.0004	0.0005
Lymphoid tumors	0.0003	0.0011	0.0004	0.0003	0.0004	0.0005
Non-Hodgkin's lymphoma (NHL)	0.0006	0.0007	0.0007	0.0004	0.0008	0.0009
Multiple myeloma	0.0006	0.0001	0.0008	0.0004	0.0008	0.0012
Lymphocytic leukemia	0.0007	0.0001	0.0007	0.0003	0.0009	0.0009
Myeloid leukemia	0.0002	0.0014	0.0016	0.0005	0.0008	0.0025
Leukemia	0.0006	0.0005	0.0007	0.0007	0.0007	0.0009
Central nervous system	0.0003	0.0019	0.0030	0.0003	0.0005	0.0024
Malignant brain neoplasm	0.0002	0.0011	0.0014	0.0002	0.0004	0.0013
Breast[c]	0.0047		0.0047	0.0001	0.0003	0.0003
Pancreas cancer	0.0006	0.0003	0.0007	0.0003	0.0007	0.0008
Stomach cancer	0.0010	0.0006	0.0011	0.0006	0.0014	0.0016

[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration.
[b] A blank cell implies that the estimated dose–response relationship was non-increasing.
[c] There were no males in the UCC cohort with a breast cancer mortality; hence, no dose–response modeling was done for the UCC cohort. There was one male in the NIOSH male cohort who had a breast cancer mortality; hence, dose–response modeling (albeit very uncertain) was done for the NIOSH male cohort.

Tables 6 and 7 show the calculated effective concentrations (ECs) and the corresponding 95% lower confidence limits (LECs), respectively, for each of the 72 combinations for an extra risk of 1/Million by age 70 years. Values in analogous tables for extra risks of 1/100,000 and 1/10,000 were approximately linearly related to those in Tables 6 and 7. The ECs and LECs are environmental concentrations in ppm. For brevity, tabled values are for models without lags. The ECs and LECs incorporate the EPA (2005b) guideline's default age-dependent adjustment factors (ADAFs) and computational procedures for age-dependent cumulative exposures (see also Sielken and Valdez-Flores, 2009a). Tabled values are for mortality and do not attempt to calculate extra risks for incidence using mortality data and incorrect formulas (see also Sielken and Valdez-Flores, 2009b).

For regulatory purposes, it is important for ECs or, more generally, points of departure (PoDs), to be well within the range of observed exposures. Table 1 shows the distributions of the observed cumulative EO exposures (ppm-days) at the end of follow up among the NIOSH females, NIOSH males, and UCC males. Table S12 in Supplemental materials shows the corresponding general location of the estimated ECs within these observed distributions. Even for extra risks as low as 1/Million, the average ECs correspond to occupational exposures that are well within the range of observed worker exposures (>10th percentile for NIOSH males or females and >2.5th percentile for UCC males). This means that, for these data, a 1/Million extra risk is an appropriate risk level for a PoD. Furthermore, even though a "unit risk" can be calculated (specifically, unit risk = (1/Million)/[EC(1/Million)]), no low-dose extrapolation is necessary to characterize exposures with extra risks down to a *de minimis* level of 1/Million.

Although excess risks are sometimes calculated for greater than 70 years (e.g., 85 years), the authors do not believe that this is appropriate for these data. The estimated exposure–response models are based on worker exposures and not older age exposures; hence, calculating extra risks through age 85 years involves an extrapolation of the fitted models beyond the range of the data upon which they are based. Furthermore, this would not be a trivial extrapolation of the proportional hazards models because the background rates are much higher beyond age 70 than below age 70. For example, the US lymphohematopoietic (LH) cancer mortality rate at age 85 is approximately 2.5 times greater than that at age 70. There is no assurance that the exposure-dependent multiplier estimated for lower ages and lower background rates would be applicable to higher ages and much higher background rates. Extending the extra risk calculation to age 85, as was done in EPA 2006, involves considerable uncertainty and is scientifically unjustified.

Table 7 shows that the statistical procedures generating the LECs are insensitive to the observed data and the observed shape of the dose–response relationship (insensitive in the sense that

even those endpoint and sub-cohort combinations with negative estimates of the slope have LECs similar to the LECs for endpoint and sub-cohorts combinations with positive estimates of the slope). The LECs are roughly the same value regardless of the magnitude of the estimated slope and regardless of whether that slope is positive or negative. (Table 4 shows whether a slope is positive or negative; Table S9 in Supplemental materials lists the slope values.) Hence, the authors believe that LECs are a poor basis for risk-management decisions for EO and have focused on ECs herein.

4. Discussion

4.1. Appropriateness of pooled analysis

All of the Cox regression results included adjustments for potential heterogeneity among studies and/or across sexes. The data were stratified by study, sex, and race where applicable, and the background hazard rates were allowed to differ by stratum during the estimation of a common slope across strata.

Potential heterogeneity between dose–response models of different studies and pooled studies was tested using DerSimonian and Laird's Q Test (also known as Cochran's Test) which found no statistically significant differences at the 5% significance level (Cochran, 1954; DerSimonian and Laird, 1986; Takkouche et al., 1999). Because we had the individual worker data available and not just the summary results of the modeling, we also tested for potential heterogeneity among dose–response models of different studies using the more powerful likelihood ratio tests. Although there were some statistically significant differences among the endpoints with negative slopes using the likelihood ratio tests, there were no statistically significant heterogeneity among dose–response models for different studies for the endpoints with positive slopes.

Using likelihood ratio tests, there were statistically significant differences between dose–response models for different sexes for six endpoints (LH, lymphoid tumors, NHL, myeloid leukemia, CNS, and malignant brain neoplasms). In the NIOSH study, either both males and females had negative estimated slopes or one sex had a positive slope and the other sex had a negative slope (Table 4). Thus, it seems to be inappropriate to characterize the risks for females based on the analysis of males and vice versa. If an inference is to be made for both males and females combined, then the PoDs based on males and females combined and adjusted for differences between sexes seems most appropriate.

The NIOSH and UCC studies defined the cause of death categories similarly and both studies included exposure estimates at the individual worker level. This and the steps taken to account for potential confounding make it reasonable to use the PoDs based on the data pooled across studies for risk assessment.

As always, for any epidemiological study, if there is an underlying exposure–response relationship, random misclassification due to errors in exposure assessment, which can diminish risk estimates, is a possibility. However, because the estimated exposure–response relationships are being used to estimate extra cancer risk, despite the lack of statistical significance of the slopes and the absence of any pattern of increase with increasing cumulative EO exposure, any concern about that exposure uncertainty masking effects is reduced.

4.2. Comparison with Steenland et al. (2004) results for the NIOSH cohort

Steenland et al. conducted Cox regressions for breast cancer, LH cancers, and "lymphoid" cancers using a variety of exposure metrics (duration, average, maximum, cumulative, and log cumulative exposure) and both continuous and categorical exposure variables. For each of these combinations, a variety of lags were also examined (no lag, 5, 10, 15, 20 years). In Steenland et al. (2004), the only dose–response models that were reported to have statistically significant positive slopes for the given exposure metric were

(1) LH cancer mortality: males, log cumulative exposure model, and 15 year lag.
(2) Lymphoid cancer mortality: males, log cumulative exposure model, and 15 year lag.
(3) Breast cancer mortality: log cumulative exposure model and 20 year lag.

No results for the standard Cox proportional hazards model (i.e., the model with the logarithm of the hazard being a linear function of the cumulative EO exposure (either lagged or unlagged)) were reported as statistically significant.

In categorical analyses, Steenland et al. (2004) reported statistically significant increases for the same three endpoints but only in the highest exposure category.

The modeling results herein for the NIOSH cohort only partially agree with those presented by Steenland et al. (2004). They agree that there are no statistically significant increases in cancer mortality with cumulative exposure to EO using either lagged or unlagged data and the standard Cox proportional hazard model. The results also agree in the sense that for the endpoints for which Steenland et al. found increases (or decreases) we also found increases (or decreases) although the numerical values were slightly different.

The only "statistically significant" positive trends reported by Steenland et al. using Cox regression were not based on the standard Cox proportional hazard model but rather were based on a log cumulative exposure model which we do not believe is an appropriate model (see Section 4.3). Furthermore, the three "statistically significant" positive trends reported by Steenland et al. (i.e., for LH, lymphoid, and breast cancer) were for lagged exposures and are not statistically significant when statistical significance is evaluated using two degrees of freedom (one for the estimated slope parameter and one for the estimated lag). (We believe that Steenland et al. incorrectly used only one degree of freedom in their evaluation of statistical significance. Steenland et al. (2004) state that "...(5, 10, 15, and 20 year lags were tried)" and "In the results we present only the lagged model with the best fit to the data, as judged by the likelihood ratio test". As illustrated in Table S10 in Supplemental materials, the value of the likelihood used in the likelihood ratio test depends on both the lag and the slope. Because of this dependence and because both the lag and the slope are found in maximum likelihood searches and not just the slope, statistical significance should be evaluated using two degrees of freedom.)

As noted above, in Steenland et al. (2004), the three dose–response models that were reported to have statistically significant positive slopes involved lags. Table S10 in Supplemental materials shows the effect of different lags on the standard Cox proportional hazards model for these three endpoints. Table S10 shows the maximum likelihood estimate of the slope parameter, the standard error, and the deviance for each of the three endpoints and each lag period (0, 5, ..., 30 years). The results in Table S10 indicate that models with 0-lag exposures fit the LH cancer and lymphoid tumors better (i.e., have smaller deviances) than the models with cumulative EO exposure lagged 5, 10, ..., 30 years. Table S10 also shows that the models with lagged exposures fit the breast cancer data better than the model with 0-lag exposures. However, the improvements in the fit (decrease in the deviance) of the models with lagged exposures for breast cancer mortality are not statistically significant at the 5% significance level.

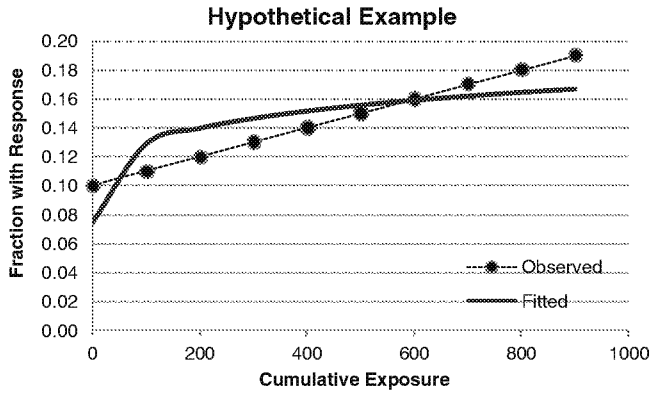

Fig. 1. Inappropriate supralinear fit when the observed data follow a linear relationship with cumulative exposure and there are equal numbers of observed person-years in each of 10 exposure intervals.

4.3. Inappropriateness of log cumulative exposure models

The "log cumulative exposure" model applied in Steenland et al. (2003, 2004) involves more than just a change in dose scale. Our concerns with the log cumulative exposure model are with the model itself and not necessarily just its use with respect to EO. Our primary concerns are (1) inappropriate supralinear fits when the observed data follow a linear or sublinear relationship with cumulative exposure; (2) the biological plausibility of supralinear models with either infinite slopes at zero or slopes at very low doses that are much greater than the slopes at slightly larger doses; (3) replacing ln(cumulative exposure) by ln(epsilon + cumulative exposure) where epsilon is arbitrarily chosen to be 1.0 or some smaller constant, and the arbitrary choice of epsilon resulting in an arbitrary choice of the slope at zero and an arbitrary choice of the low-dose behavior of the fitted model; (4) even when supralinearity is seemingly suggested by the observed data, the supralinearity may be the result of an artifact such as using an inappropriate dose metric (e.g., administered dose instead of delivered dose) or exposure misclassification; (5) the amount of forced supralinearity being arbitrarily determined by the choice of exposure scale (for example, $\mu g/m^3$-years, mg/m^3-years, or g/m^3-years); and (6) the shape of the fitted model not changing substantially with changes in the observed data especially at the low to middle exposure levels.

The Cox proportional hazards model incorporating log cumulative exposure in Steenland et al. (2004) has the following general form:

$$\text{Fraction response at cumulative exposure } X = \text{Beta0} \times \exp[\text{Beta1} \times \ln(1+X)] = \text{Beta0} \times [1+X]^{\text{Beta1}},$$

where the parameters Beta0 (the background response rate) and Beta1 (the power) are restricted to non-negative values. The form of this model forces the fitted dose–response model to be supralinear regardless of the observed response data. Fig. 1 provides a simple hypothetical example illustrating the inappropriateness of the model.

Another way to understand the forced supralinearity (Beta1 < 1.0) is as follows. The general model above can be rewritten in terms of rate ratios (RRs) as

$$(\text{Fraction response at cumulative exposure } X)/\text{Beta0} = \text{RR} = [1+X]^{\text{Beta1}}.$$

RRs are of concern when they exceed 1 but rarely are they very large, say greater than 10. However, cumulative exposure (ppm-days or ppm-years) can easily be in the 100s or the 1000s or larger. For example, the only way that an RR can be less than 10, if $X = 1000$, is for Beta1 to be substantially less than 1 (in fact, Beta1 has to be less than or equal to $\ln(10)/\ln(1001) = 0.3333$) in which case the model is forced to be supralinear.

Table S11 in Supplemental materials indicates that the fit (maximum likelihood) varies depending upon the exposure scale used in the log cumulative exposure model (i.e., ppm-days, ppm-years, ppb-days, and ppb-years). Table S11 also illustrates that the Cox proportional hazard model with the slope parameter multiplying cumulative EO exposure fits the data better than any of these four alternative log cumulative exposure models in more than 55% of the combinations of 12 endpoints and six sub-cohorts analyzed.

4.4. Comparison with EPA 2006 draft risk characterization

The EPA 2006 draft assessment shows an LEC(1/100) of 0.00608 ppm for 85 years for LH which is equivalent to 0.014 ppm for 70 years using their life-table calculator. Table S13 in Supplemental materials shows the ratio of the LECs for an extra risk of 1/100 from our Cox proportional hazards modeling to that 0.014 ppm. The average ratio ranges between 100 and 300 depending on the sub-cohort. Although the authors would disagree with the appropriateness of using an LEC(1/100) as a PoD for EO, the magnitude of the ratios in Table S13 in Supplemental materials indicate the impact of how the exposure–response modeling and excess risk characterization is carried out.

More important than the comparison of LEC(1/100)s, even the smallest EC(1/Million) in Table 6 (namely, 0.0006 ppm or 600 ppt) is more than 1500 times larger than the 2006 EPA value for the lifetime chronic EO exposure level corresponding to an increased risk of 1/Million. EPA's 2006 draft value is 0.0007 $\mu g/m^3$ which is equivalent to 0.00038 ppb (using 1 ppb EO = 1.83 $\mu g/m^3$) or approximately 0.4 ppt. The 0.0006 ppm = 0.6 ppb = 600 ppt divided by 0.4 ppt is 1500. The breakdown of the source of the difference is approximately as follows:

(1) 150-fold for our Cox proportional hazards modeling of specific data for individual workers versus EPA's draft linear modeling of summary odds ratios, and our evaluation of mortality versus EPA's evaluation of incidence.
(2) 1.6-fold for our direct evaluation of extra risks of 1/Million instead of EPA's linear extrapolation below an extra risk of 1/100.
(3) 2-fold for our use of ECs versus EPA's reliance on LECs.
(4) 2.3-fold for our assessing extra risk at age 70 instead of EPA's 85 years.
(5) 1.66-fold for correctly implementing EPA's (2005b) guidelines for ADAFs.

If these differences were independent (which they are not), they would have compounded to more than 1800 ($150 \times 1.6 \times 2 \times 2.3 \times 1.66 > 1800$).

Some of the differences between our risk characterizations and those in the EPA 2006 draft assessment are a matter of EPA policy such as the use of LECs rather than ECs and the use of 70 years instead of 85 years.

5. Conclusions

In the analyses of the NIOSH cohort, the updated UCC cohort, and the pooled studies of over 19,000 workers, none of the SMRs for any combination of the 12 cancer endpoints and six sub-cohorts analyzed were statistically significantly greater than one

including the ones of greatest previous interest: leukemia, lymphohematopoietic tissue, lymphoid tumors, NHL, and breast cancer.

The analyses presented herein fit Cox proportional hazards models with cumulative EO exposure (ppm-days) as the linear predictor to six sub-cohorts (NIOSH males, UCC males, NIOSH and UCC males, NIOSH females, NIOSH males and females, and NIOSH and UCC males and females). None of these models found statistically significant increases in any of the 12 cancer mortality types with increased cumulative EO exposure at the 5% significance level. Furthermore, if "any increases" are evaluated instead of just "statistically significant increases," then none of the endpoints had an increase for every sub-cohort. Thus, there was not even a consistent indication among the six sub-cohorts of the direction of an effect.

As in Steenland et al. (2004) and Swaen et al. (2009), the Cox proportional hazards models presented here with cumulative EO exposure treated as a continuous variable and the linear predictor indicate that there are no increasing trends in the hazard rates with increasing cumulative EO exposure. The lack of increasing trends is corroborated by categorical analyses which compared the hazard rates at different quintiles to the hazard rate at the lowest quintile.

Our Cox proportional hazards modeling based on individual worker data and cumulative EO exposure as a continuous exposure metric yields substantially different estimates of risks than EPA's models based on summary odds ratios in their 2006 draft assessment. Our modeling estimates of ECs in Table 6 corresponding to a 1-in-a-million excess environmental cancer risk are more than 1500-fold greater than the 0.4 ppt in EPA's 2006 draft IRIS risk assessment.

There is no statistically significant heterogeneity between the dose–response models of the two studies and the dose–response model of the pooled studies. Combining studies increases power. For males, the estimates of the EC(1/Million) for endpoints with a positive slope based on the pooled data across studies and including an adjustment for potential differences between studies range from approximately 0.001 to 0.003 ppm and average approximately 0.002 ppm. The same range and average applies to females in the NIOSH study. However, the endpoints with positive slopes for females have negative slopes for males, and the endpoints with positive slopes for males have negative slopes for females. An EC(1/Million) of 0.001 ppm (1 ppb or 1.83 $\mu g/m^3$) corresponds to a potency value of approximately 5×10^{-7} per $\mu g/m^3$.

Because the statistical procedures generating the LECs are insensitive to the observed data and the observed shape of the dose–response relationship, and because the estimates of the EC (1/Million) are based on human data and are well within the heart of the observed epidemiological exposure data, the EC (1/Million), ranging between 0.001 and 0.003 ppm, is an appropriate point of departure for risk characterization of EO.

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Dr. Sielken gave a related presentation entitled "Use of Pooled Epidemiology Data in Quantitative Risk Assessment" at the Toxicology Forum on July 15, 2009.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yrtph.2009.10.001.

References

Cochran, W.G., 1954. The combination of estimates from different experiments. Biometrics 10, 101–129.

Delzell, E., 2009. Presentation entitled "The Impact and Importance of New Epidemiology on EO Hazard Characterization" to appear as part of the Proceedings of the Toxicology Forum on July 15, 2009.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188.

Greenberg, H.L., Ott, M.G., 1990. Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: a mortality study. Br. J. Ind. Med. 47, 221–230.

Greife, A.L., Hornung, R.W., Stayner, L.T., Steenland, K., 1988. Development of a model for use in estimating exposure to ethylene oxide in a retrospective cohort mortality study. Scand. J. Work Environ. Health 14, 29–30.

Hagmar, L., Mikoczy, Z., Welinder, H., 1995. Cancer incidence in Swedish sterilant workers exposed to ethylene oxide. Occup. Environ. Med. 52, 154–156.

Hogstedt, C., Rohlen, O., Berndtsson, B.S., Axelson, O., Ehrenberg, L., 1979. A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br. J. Ind. Med. 36, 276–280.

Hornung, R.W., Greife, A.L., Stayner, L.T., Steenland, K., Herrick, R.F., Elliott, L.J., Ringenburg, V.L., Morawetz, J., 1994. Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. Am. J. Ind. Med. 25, 825–836.

Kirman, C.R., Sweeney, L.M., Teta, M.J., Sielken, R.L., Valdez-Flores, C., Albertini, R.J., Gargas, M.L., 2004. Addressing nonlinearity in the exposure–response relationship for a genotoxic carcinogen: cancer potency estimates for ethylene oxide. Risk Anal. 24 (5), 1165–1183.

Marsh, G.M., Youk, A.O., Stone, R.A., Sefcik, S., Alcorn, C., 1998. OCMAP-PLUS: a program for the comprehensive analysis of occupational cohort data. J. Occup. Environ. Med. 40, 351–362.

Shore, R.E., Gardner, M.J., Pannett, B., 1993. Ethylene oxide: an assessment of the epidemiological evidence on carcinogenicity. Br. J. Ind. Med. 50, 971–997.

Sielken Jr., R.L., Valdez-Flores, C., 2009a. Calculating excess risk with age-dependent adjustment factors and cumulative doses: ethylene oxide case study. Regul. Toxicol. Pharmacol. 55, 76–81.

Sielken Jr., R.L., Valdez-Flores, C., 2009b. Life-table calculations of excess risk for incidence versus mortality: ethylene oxide case study. Regul. Toxicol. Pharmacol. 55, 82–89.

Steenland, K., Spaeth, S., Cassinelli, R., et al., 1998. NIOSH life table program for personal computers. Am. J. Ind. Med. 34, 517–518.

Steenland, K., Stayner, L., Deddens, J., 2004. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup. Environ. Med. 61, 2–7.

Steenland, K., Stayner, L., Griefe, A., Halperin, B., Hayes, R., Hornung, R., Nowlin, S., 1991. A cohort mortality study of workers exposed to ethylene oxide. N. Engl. J. Med. 324 (20), 1402–1407.

Steenland, K., Whelan, E., Deddens, J., Stayner, L., Ward, E., 2003. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women. Cancer Causes Control 14, 531–539.

Swaen, G.M., Burns, C., Teta, J.M., Bodner, K., Keenan, D., Bodnar, C.M., 2009. Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J. Occup. Environ. Med. 51 (6), 714–723.

Takkouche, B., Cadarso-Suarez, C., Spiegelman, D., 1999. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. Am. J. Epidemiol. 150, 206–215.

Teta, M.J., Benson, L.O., Vitale, J.N., 1993. Mortality study of ethylene oxide workers in chemical manufacturing: a mortality study. Br. J. Ind. Med. 50, 704–709.

Teta, M.J., Sielken, R.L., Valdez-Flores, C., 1999. Ethylene oxide cancer risk assessment based on epidemiologic data: application of revised regulatory guidelines. Risk Anal. 19, 1135–1155.

US EPA, 2005a. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. US Environmental Protection Agency, Risk Assessment Forum, March, 2005.

US EPA, 2005b. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/360/R-03/003F. US Environmental Protection Agency, Risk Assessment Forum, March, 2005.

US EPA, 2006. Evaluation of the Carcinogenicity of Ethylene Oxide. EPA/635/R-061/003. External Review Draft. US Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development, Washington, DC, August, 2006. Available from: <http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=157664/>.